Do Antipsychotic Medications Decrease the Risk of Suicide in Patients With Schizophrenia?

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The lifetime risk of suicide in persons with schizophrenia is much greater than that in the general population. The role of antipsychotic medications in decreasing suicide risk in schizophrenia has been little studied, and results often appear inconclusive and even confusing when issues such as dose-response effect are examined. Yet, evidence exists that both the traditional and newer antipsychotic medications reduce the risk of suicide and suicide attempts in schizophrenia. Because side effects are potentially significant risk factors in suicide, considerable incentive exists to examine whether newer antipsychotic agents that have a lower incidence of extrapyramidal side effects offer greater safety for this population.

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Individuals with schizophrenia kill themselves at a much greater rate than the general population. The lifetime risk of suicide* for schizophrenia has been estimated at about 10% to 13%, with an incidence of 350–600/100,000, compared with 11.4/100,000 in the general population.[1] Suicide has an economic cost in addition to its human burden. For schizophrenia, the estimated cost of treating suicide attempts and investigating completed suicides is about $190 million per year. The cost associated with lost productivity from individuals who commit suicide has been estimated at $7 billion per year.[2]

Antipsychotic medications are the standard treatment for schizophrenia, and one of the many reasons they are valued is that they are thought to decrease the risk of violence and perhaps suicide. Surprisingly, however, very few controlled studies examine whether antipsychotic medications do decrease the risk of suicide in patients with schizophrenia. This review brings together what few data exist from controlled studies regarding the benefits provided by antipsychotic medications against suicide and suicide attempts in schizophrenia.

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RISK FACTORS FOR SUICIDE IN SCHIZOPHRENIA

One issue central to suicide prevention is the identification of risk factors. Knowing these can help clinicians decide which patients are at greatest risk for suicide and suicide attempts. Our knowledge about suicide in schizophrenia is surprisingly limited given the high rate of suicide associated with the disorder. Nevertheless, comprehensive reviews have identified a number of putative risk factors.[1,3–5] Not surprisingly, patients with schizophrenia appear to have several risk factors in common with the general population; for instance, in both populations being white, being male, being depressed, being unmarried, being unemployed, and living alone or being socially isolated add to the risk of suicide.[4]

A number of risk factors also appear to be specific to individuals with schizophrenia compared with the general population. For instance, most schizophrenics commit suicide at a relatively young age, whereas in the general population the highest risk of suicide is found in individuals over the age of 65.[6] In a study that identified mortality and causes of death in first-admission schizophrenic patients in Denmark, Mortensen and Juel (1993)[7] found that schizophrenic patients between the ages of 20 and 29 were at greatest risk for committing suicide. Other studies have similarly found that younger schizophrenic patients have the highest risk of suicide.[4,8]

Although patients with schizophrenia are at a greater risk of killing themselves within the first 10 years of their

*Throughout this article, the term *suicide* is synonymous with a completed suicide. Findings from studies that focused on attempted, rather than completed, suicide are identified accordingly.

illness,[8–12] it is less clear what their state of illness is likely to be when they commit suicide. Drake and Cotton (1986)[13] described schizophrenic patients who committed suicide as having numerous relapses and remissions, but noted that at the time of suicide none were experiencing an active psychosis. Only 3 of 20 patients who committed suicide in a study by Breier and Astrachan (1984)[8] had an acute exacerbation of psychosis at the time of suicide. At least 36% of the patients in a 1989 study by Cheng and colleagues[14] were felt to be in remission at the time of suicide. In contrast, Heilä and colleagues (1997)[15] found that most of their patients were suffering from either an active illness or an acute exacerbation of a chronic illness at the time of suicide.

A chronic course of illness has also been linked to increased risk of suicide in schizophrenic patients.[8,9,13,16,17] Because most of the studies that looked at the issue of chronicity and suicide were hospital-based, patients without a hospitalization, such as patients very early in the course of their illness or homeless individuals, may not be represented in the findings. In fact, we do not know the risk of suicide during the extremely early phases of the illness, such as before an individual receives a formal diagnosis of schizophrenia.

Although a number of these variables are, statistically speaking, risk factors for suicide in schizophrenia, few are of value to clinicians if used alone. For instance, because relatively few patients with schizophrenia marry, being unmarried is more likely to be associated with a diagnosis of schizophrenia than with suicide risk. Being unemployed, young, and having a chronic course of illness are other extremely common features of schizophrenia and thus clinically unlikely to be much help in distinguishing those at risk for suicide. On the other hand, several factors may be of clinical use in determining who is at greatest risk for suicide. For instance, most studies have consistently shown that a prior history of suicide attempts is one of the strongest risk factors for completing suicide in schizophrenia.[8,11,12,16]

Another potentially important risk factor is the presence of depression or a feeling of hopelessness,[9,18–22] although not all studies have found it to be predictive of suicide or suicide attempts.[11,12,16,23]

From a public health perspective, perhaps the most important risk factor for suicide in schizophrenia occurs when there is a change in hospital status. One follow-up study of over 9000 first-admission patients with schizophrenia found that the periods of greatest risk for suicide were shortly after admission, during periods of temporary leave from the hospital, and for a month following discharge.[24]

SUICIDALITY AND ANTIPSYCHOTIC MEDICATIONS

In conjunction with other treatments, antipsychotic medications are commonly used to decrease the risk of suicide in patients with schizophrenia. During the first few years after their introduction, there was concern that rather than decreasing the risk of suicide among patients with schizophrenia, antipsychotic medications might either have no effect[25] or actually increase the risk.[26,27] Beisser and Blanchette (1961)[26] studied suicide in all psychiatric patients at the Metropolitan State Hospital (Norwalk, California) between 1916 and 1958 and found little change in the rate of suicide; however, an increase in the suicide rate was observed in 1957, the year antipsychotic medications were introduced to Metropolitan State Hospital. Beisser and Blanchette noted that the patients who committed suicide were more likely to be depressed; however, they also found that many of them had been given reserpine, a medication that became a pharmacologic model for depression.

Hussar (1962)[27] similarly found that the rate of suicide in all psychiatric patients at the Montrose Veterans Administration Hospital increased following the introduction of antipsychotic medications in 1955. One explanation put forth for the apparent increase in suicide associated with antipsychotic medications was that they enable patients to live in less restrictive environments, which in turn provide more opportunities for patients to kill themselves.[27–29]

This early idea that treating patients with antipsychotic medications increased the rate of suicide in schizophrenia was not found in subsequent studies. Kline (1959)[30] found no increase in the suicide rate in a large, diagnostically mixed group of patients treated with antipsychotic medications. When Cohen and colleagues (1964)[29] performed one of the first controlled studies regarding this issue, they found that patients with schizophrenia dying from suicide were no more likely to be receiving antipsychotic medications than a matched control group, and their daily doses were equivalent. They further found that antipsychotic medications did not increase the incidence of depression, although depression was more common in the patients who killed themselves. Cohen and colleagues suggested that the use of antipsychotic medications may have produced a false optimism in the hospital staff responsible for the patients, perhaps leading to premature release. Another indication of this was that a number of suicides occurred soon after the patients' medications were abruptly discontinued.

In a study by Wilkinson and Bacon (1984),[17] as many patients with schizophrenia who committed suicide were taking antipsychotic medications as those in a control group of patients who did not commit suicide. Antipsychotic medications did, however, appear to prevent suicide attempts. In that study, 30 (67%) of 45 patients who attempted suicide were taking antipsychotic medications, while 43 (96%) of 45 control patients were taking antipsychotic medications ($p < .002$).

One of the better controlled studies examining the relationship between antipsychotic medications and suicide (more specifically suicide attempts) is that of Johnson and colleagues (1983).[31] Patients who had been stable for 12 to

48 months while being treated with antipsychotic medications were divided into a control group who continued taking medications and a group for whom medications were discontinued. Johnson and colleagues found that patients with chronic schizophrenia who stopped taking antipsychotic medications had substantially more suicide attempts than controls. During an 18-month interval, 27% of the group not taking antipsychotic medications attempted suicide compared with 11% of the control group ($p < .05$).

If antipsychotic medications decrease the risk of suicide, a dose-response relationship might be expected, with higher doses decreasing the risk. On the other hand, the use of antipsychotic medications has often been associated with problematic side effects, many of which are also dose related. Perhaps the most significant potential side effect for suicide, besides depression, is akathisia, which has been associated with suicide in several case reports.[32–35] Significantly, violence directed at others has also been associated with akathisia.[35,36] Finally, studies that looked at the relationship between suicide and another serious side effect of antipsychotic medications, tardive dyskinesia (which is not strictly speaking dose related), have obtained mixed results (reviewed by Yassa and Jones, 1985[37]).

Further complicating this issue is that the more symptomatic patients are likely to be receiving the highest doses of antipsychotic medications. Thus, instead of the relationship between suicide and dose (or blood level) being linear, it might be expected to be an inverted "U." Very low doses would be ineffective at preventing suicide, and higher doses, because they are associated either with side effects or with a more severe illness, might also be associated with higher suicide rates. On the basis of these assumptions, the literature on antipsychotic medications and suicide might be expected to be confusing; it is.

Two studies seem to support the notion that there might be a dose-response effect. Warnes (1968)[38] found that patients with schizophrenia who killed themselves were taking significantly lower doses of antipsychotic medications than patients who did not kill themselves. Taiminen (1993)[39] studied a diagnostically mixed group of patients who committed suicide and also found that the patients who committed suicide tended to be taking lower doses of antipsychotic medications than a control group who did not, although the difference was not statistically significant.

In contrast, higher doses of antipsychotic medications have also been associated with suicide. Hogan and Awad (1983)[40] found that the association of suicide to the dose of antipsychotic medication was restricted to those patients taking depot fluphenazine (they found no relationship between the dose of antipsychotic medication and suicide for trifluoperazine, perphenazine, chlorpromazine, and haloperidol). However, the 16 patients who committed suicide while taking fluphenazine enanthate were uniformly taking higher doses than the 11 control patients taking the same medication. Interestingly, extrapyramidal side effects were more frequent in the patients who committed suicide, but a concurrent affective disturbance was not found. Cheng and colleagues (1990)[12] studied a group of schizophrenic patients and found no difference between those who committed suicide and those who did not, with the exception that those patients who committed suicide were taking higher doses of antipsychotic medication at the time of death.

If the connection between suicide and antipsychotic medications is due to extrapyramidal side effects and akathisia, then one might expect the newer antipsychotic medications, which have a lower incidence of extrapyramidal side effects, to also have a lower risk of suicide associated with them. To date, several studies support this notion, although the reason for the decrease in suicide and suicide attempts is not clear. Beasley and colleagues (1998)[41] found that olanzapine, which produces relatively few extrapyramidal side effects, had a greater effect in reducing suicidal thoughts than haloperidol.

Two other studies have found that clozapine, which produces the least extrapyramidal side effects of any antipsychotic medication, reduced the rate of both suicide attempts and suicide.[42,43] Meltzer and Okayli (1995)[42] compared the rate of suicide attempts in patients before and after they were treated with clozapine. In 88 treatment-resistant schizophrenic patients, they found that clozapine led to a statistically significant reduction in the rate of suicide attempts. Clozapine treatment reduced the seriousness and lethality of attempts and reduced positive symptoms. Relief from depression, hopelessness, helplessness, and suicidality, as measured by the Hamilton Rating Scale for Depression, was also statistically significant. Meltzer and Okayli suggested that clozapine's ability to provide relief from tardive dyskinesia and to treat the symptoms of schizophrenia without producing the extrapyramidal side effects associated with traditional antipsychotic medications might have contributed to the reduction in suicidality.

Using the Clozaril National Registry, Walker and colleagues (1997)[43] identified 67,000 patients who were either currently taking clozapine or had been treated with it in the past. These patients were cross-matched with the Social Security Administration Death Master Files and National Death Index. From these files, they were able to compare the number of deaths for patients who were currently using clozapine with the number for those who had used it recently (within the previous 3 months) or in the past (clozapine not used for 3 or more months). They found that mortality rates for patients aged 10 to 54 were lower during current clozapine use than during periods of nonuse. The suicide rate per 100,000 persons was 39 for current clozapine users, 246 for recent users, and 222 for past users. The authors felt that although a decreased incidence of suicide during clozapine use might have been due to the antipsychotic and/or antidepressive properties of clozapine, it was possible that the absence of antipsychotic-

induced parkinsonism, akathisia, and tardive dyskinesia reduced the rate of suicide.

CONCLUSIONS

In terms of preventing suicide in schizophrenia, the role of antipsychotic medications has been a largely neglected area of study. Even among the studies that seem to address this issue, several are not specific to schizophrenia, and the results of others appear to be inconclusive. Nevertheless, as the studies reviewed above suggest, the use of antipsychotic medications in schizophrenia probably decreases the risk of suicide. Several studies showed that both the traditional and newer antipsychotic medications reduce the risk of suicide and suicide attempts in schizophrenia.

Although no universal agreement exists about which risk factors are most important for predicting suicide in schizophrenia, individuals that have a number of risk factors may need to be monitored more carefully. Also, any of the risk factors for suicide in the general population might be encountered in the schizophrenic population, in addition to those specific to the illness. For example, even though the maximum risk for suicide in schizophrenia occurs at an early age (which is closely related to the duration of illness), there is no reason to believe that individuals over 65 might not be affected by the same heightened risk factors that impact the general population.

As new, perhaps more efficacious, and certainly more expensive antipsychotic medications are introduced, there is considerable incentive to determine whether they are safer. Thus, over the next few years, we should learn a great deal about suicide in schizophrenia, and perhaps about better ways of preventing it.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon), reserpine (Serpasil and others), trifluoperazine (Stelazine).

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